Arguments/Remarks

Favorable consideration of this application is respectfully requested in view of the foregoing amendments and the following remarks. Claims 8-10, 13, and 15 are pending in the application. Each of the claims currently stand rejected. No new matter has been added.

Rejection Under 35 USC §103(a), Obviousness

Claims 8-10 and 13-15 are rejected under 35 U.S.C. §103(a), as being unpatentable over Billich (US patent 5,538,997)(hereafter, "Billich reference") in view of Habich (US patent 5,633,231)(hereafter, "Habich reference") and Scholz (D Scholz et al., J. Med. Chem. (1994) 37, 3079)(hereafter, "Scholz reference"). Specifically, the Examiner posits that Billich teaches the instantly claimed compound (example 11) where the only difference is the N-protecting, and that modification using Habich and Scholz is an obvious alteration to arrive at the claimed compounds. Applicants disagree.

The Examiner has not established a *prima facia* case of obviousness. The Federal Circuit recently addressed obviousness of closely-related chemical structures in *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492. F.3d 1350 (Fed. Cir. 2007). Specifically citing their decision of *In re Deuel*, 51 F3d 1552, the Court stated, "A known compound may suggest its homolog, analog, or isomer because such compounds 'often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties'." The Court clarified however, "that in order to find a prima facie case of unpatentability in such instances, a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required."

The Court further held in *Takeda*, "Thus in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish a prima facie obviousness of a new claimed compound."

Still further, the CAFC has elucidated the obviousness factors for chemical structures in *Eisai v. Dr. Reddy's Laboratories* (533 F.3d 1353) (Fed. Cir. 2008). The CAFC discussed the *Graham* factors in new chemical composition cases, stating, "Post-KSR, a prima facia case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound."

It is therefore necessary that in order to establish a prima facia case of obviousness for a chemical composition of matter, it is necessary to establish a lead compound from the prior art. It is further necessary to establish a showing that the prior art would have suggested making the specific molecular modifications to the lead compound necessary in order to achieve the claimed invention.

In the present case, the Examiner has neither identified a "lead compound," nor identified a teaching in the art which would lead one of skill in the art to make the modifications to arrive at the claimed invention. In the absence of such an analysis, a *prima facia* case of obviousness has not been established.

As the Examiner states, the compounds of Billich et al are contemplated as HIV inhibitors. In contrast to that, the compounds of the present invention have found to be useful for the treatment of a proliferative disease, e.g. of a solid tumor. Billich et al exemplifies 61 compounds, only 5 of which (Examples 4, 11, 21, 22 and 30) show the (non chiral) "2-hydroxybenzyl substituted in 4 position by methoxy" as residue R4. The vast majority of compounds (49) possess a 2(R)--hydroxyindan-1(S)-yl residue at position R4. The compounds with the (chiral) 2(R)--hydroxyindan-1(S)-yl residue at position R4 are the only claimed compounds. There is no analysis to support that one of these 5 compounds would be a "lead compound."

Scholz et al, J.Med.Chem 1994, 37, 3079-3089 also teaches compounds as HIV inhibitors. In contrast to that the compounds of the present invention have found to be useful for the treatment of a proliferative disease, e.g. of a solid tumor. Scholz et al determined, that replacement of the aminobenzyl group (substituent R, general structure of table 5) by a benzimidazoyl moiety leads to a 4 times more potent compound ("major increase in potency") (compound 44 vs 6), (Page 3083, table 5 and discussion). The benzimidazoyl moiety is also present in the most active compound 50.

The teachings of Scholz combined with Billich therefore teach one of skill in the art away from (simpler) benzyl derivatives towards bicyclic moieties which are either chiral or heterocyclic, particularly for treatment of HIV, which the references disclose.

The Examiner further discounts the use of the compounds in treating HIV as not being relevant because applicants are not claiming a method of treatment. Applicants disagree. In analyzing prior art for obviousness, the total teaching of the reference must be considered. Because a compound may be useful for treatment for one particular disease is not an indicator

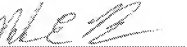
for usefulness in treating another disease. Still further, the teaching of the use of compounds for one indication may lead to molecular modifications unnecessary and not helpful in a different indication. In fact, disparate disease indications typically include different biological targets and mechanism of actions with little commonality. The use of the compounds of the prior art in treating HIV is therefore relevant because the modifications used to arrive at the presently claimed compounds may not have been contemplated for treatment of HIV.

Applicants respectfully request entry of the amendments to the claims and the specification and submit no new matter is added thereby. Should the Examiner have any questions, please contact the undersigned attorney.

However, if it is deemed that additional fees are required, the Commissioner is authorized to charge Deposit Account No. 504409 in the name of Novartis for any fees due.

In view of the above, an early Notice of Allowance is respectfully requested.

Respectfully submitted,



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